Remarks

Reconsideration of this Application is respectfully requested.

I. Status of the Claims

Claims 15-28 are pending in the application, with claim 15 being the independent claim. Claims 15, 16 and 17 are sought to be amended. These changes are believed to introduce no new matter, and their entry is respectfully requested.

II. Summary of the Office Action

In the Office Action dated October 2, 2001, the Examiner has made two rejections of the claims. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

III. Support for Amended Claims

Support for amended claim 15 can be found, *inter alia*, in the specification at page 4, lines 25-31 and at page 5, lines 10-12. Support for amended claims 16 and 17 can be found, *inter alia*, at page 4, lines 33-34.

IV. Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 15-28 under 35 USC § 103(a) as allegedly being unpatentable over Porgador *et al.*, *J. Immunol. 150*:1458-1470 (1993) ("Porgador") in view of Saravolac *et al.*, *Antiviral Res. 29*:199-207 (1996) ("Saravolac"), or Cleland and Jones, *Pharm. Res. 13*:1464-1475 (1996) ("Cleland"), or Fujioka *et al.*, *J. Controlled Release 33*:317-323 (1995) ("Fujioka"). *See* Paper No. 8, page 2. According to the Examiner,

> [i]t would have been obvious to one of ordinary skill in the art at the time of the claimed invention to combine the teachings of Porgador et al and Saravolac et al or Cleland et al or Fujioka et al to produce a vaccine composition comprising the tumor antigens and slow release systems delivering IFN-γ.

Paper No. 8, page 3. Applicants respectfully disagree with this assessment and traverse this rejection.

In order to establish a *prima facie* case of obviousness, three requirements must be met. First, all the claim limitations must be taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Third, there must be a reasonable expectation of success. *See In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicants' disclosure. *See In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In view of the above prerequisites, Applicants present the following remarks demonstrating that a *prima facie* case of obviousness has not been established for the present claims.

A. The References Do Not Teach or Suggest All of the Claim Limitations

The references cited by the Examiner, either alone or in combination with one another, do not teach or suggest all of the limitations found in Applicants' claims. Specifically, none of the references teach or suggest a tumor antigen source as a separate and distinct element from a IFN-γ delayed release system as required by the present claims. The importance of this aspect of the invention is expressed in the specification as follows:

> The problem of the present invention was to provide an alternative tumour vaccine which is easy to produce, which makes it possible to release the immunostimulant cytokine in [a] controlled manner at the vaccination site in the therapeutically effective dosage range over a fairly long period.
>
> This problem is solved according to the invention with a tumour vaccine based on tumour antigens, which is characterised in that it contains as active ingredient, *in addition to a tumour antigen source*, a release system with delayed release of the active substance for IFN-γ, the effective dosage of IFN-γ being 50 ng to 5 μg and the release interval being from half an hour to 8 days.

Specification at page 4, lines 18-31 (emphasis added).

Porgador teaches a lung tumor cell line (D122) that is infected with a retroviral vector that expresses the IFN-γ gene. *See* Porgador at page 1461, right column, lines 34-46. There is no teaching or suggestion in Porgador of using a tumor antigen source that is separate and distinct from a release system with delayed release of IFN-γ. In fact, the principle purpose for creating the transfected cell line in Porgador appears to be simply to

establish a source of IFN-γ, not to exploit the cell line as a tumor antigen source. As stated in Porgador, "[i]n the present study, we seek to further explore the antitumor potential of tumor cells manipulated to secrete IFN-γ after gene transfer, using a model of the high-metastatic 3LL-D122 tumor." Porgador at page 1459, left column, lines 18-21. Moreover, the cell line used in Porgador is described as "poorly immunogenic," *see id.* at page 1459, right column, lines 17-18, indicating that the transfected cells are not intended to serve as an antigen source.

The development of a tumor vaccine comprising, in addition to a tumor antigen source, a release system with delayed release of IFN-γ, is an important technological advance over previously described tumor vaccines, including those that use genetically modified tumor cells. For instance, as stated in the specification:

> A tumour vaccine based on tumour antigens, *e.g.* in the form of tumour cells, in conjunction with a "slow release" system in which IFN-γ is incorporated has the advantage, over tumour vaccines from gene-modified tumour cells which express IFN-γ, [in] that the release of cytokine is precisely controlled at the vaccination site and hence the cytokine is administered in an accurate and reproducible dosage. Moreover, the labour and hence costs involved in the manufacture are substantially reduced.

Specification at page 9, line 30, through page 10, line 3.

Like Porgador, the other references cited by the Examiner also fail to teach or suggest a tumor antigen source as a separate and distinct element from a IFN-γ delayed release system. In fact, the teachings of Saravolac, Cleland and Fujioka are completely silent with regard to a tumor antigen source. Saravolac describes the use of liposome-encapsulated IFN-γ *by itself* for purposes of evaluating "the effectiveness of a liposome delivery system in potentiating the antiviral as well as immunomodulatory activities of IFN-

γ." *See* Saravolac at page 200, right column, lines 14-18. Cleland describes the incorporation of IFN-γ into microspheres and focuses on maintaining the stability of proteins during the microencapsulation process, *i.e.*, preventing protein denaturation. *See* Cleland at page 1464, left column (abstract), lines 1-7. The only inferred biological use for such IFN-γ-containing microspheres in Cleland is the *in vitro* protection of cultured cells from viral killing. *See id.* at page 1466, right column, lines 43-56. Finally, Fujioka describes minipelets containing "IFN." Applicants note that the interferon described in Fujioka is not IFN-γ, but IFN-α. *See* Fujioka at page 318, right column, lines 28-31 ("... a natural *alpha-type* IFN, was prepared from Sendai virus-induced human Namalwa cells and purified..." (emphasis added)). In addition to the fact that Fujioka does not teach an IFN-γ release system, Applicants further note that there is no teaching or suggestion in Fujioka that the minipellets described therein can be used in the context of a tumor vaccine.

In sum, because none of the references cited by the Examiner teach or suggest a tumor antigen source as a separate and distinct element from a IFN-γ delayed release system, the references, alone or in combination, do not teach or suggest all of the limitations of Applicants' claims. As such, under *Royka*, a *prima facie* case of obviousness has not been established.

B. There is No Suggestion or Motivation to Combine the References

Applicants have established above that the references cited by the Examiner fail to teach all of the elements of Applicants' claims. Therefore, it follows that a combination of the reference teachings would *not* lead one of ordinary skill in the art to Applicants' claimed invention. Notwithstanding this fact, Applicants also contend that neither the references themselves, nor the knowledge generally available to those of ordinary skill in the art,

provide a suggestion or motivation to modify the cited references or to combine reference teachings.

The Examiner provides the following explanation as to why the skilled artisan would allegedly be motivated to combine the teachings of Porgador with that of Saravolac, Cleland or Fujioka:

> One [o]f ordinary skill in the art would have been motivated to [combine the reference teachings] because it would be definitely advantageous to have a source of IFN-γ in a slow release system that would be available readily to mix with tumor antigen where there is a need to change the tumor antigen. By having a ready source of the cytokine release system, one of ordinary skill in the art would know that the only variable would be the source of antigen to be added to the composition, and therefore the process of preparing these vaccines is simplified.

Paper No. 8, page 3.

Applicants respectfully remind the Examiner that the requisite motivation for establishing a *prima facie* case of obviousness must be found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *See In re Kotzhab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000). Moreover, the mere fact that an advantage *might* be realized by combining reference teachings does not mean that a skilled artisan would be motivate to do so. *See In re Mills*, 916 F.2d 680,682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1992) (Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so.")

The Examiner, rather than pointing to anything specific in the references or in the general knowledge of those skilled in the art, has simply asserted that "it would be definitely

advantageous to have a source of IFN-γ in a slow release system that would be available readily to mix with tumor antigen where there is a need to change the tumor antigen." The fact that something may be "advantageous," (an unsupported proposition) however, does not indicate motivation for § 103 purposes under *Mills*. Moreover, the Examiner's statement that "[b]y having a ready source of the cytokine release system, one of ordinary skill in the art would know that the only variable would be the source of antigen to be added to the composition, and therefore the process of preparing these vaccines is simplified," assumes the existence of at least some motivation to produce a vaccine in the first place. The Examiner, however, has not pointed to any such motivation.

Applicants submit that, upon careful analysis of the cited references, the skilled artisan would find no motivation to combine or modify the reference teachings to arrive at a tumor vaccine that falls within the scope of the present claims. Accordingly, under *Vaeck*, a *prima facie* case of obviousness has not been established.

C. Summary

None of the references cited by the Examiner teach or suggest a tumor antigen source as a separate and distinct element from a IFN-γ delayed release system as required by the present claims. In addition, neither the references cited by the Examiner nor the knowledge generally possessed by those of ordinary skill in the art provide any motivation to combine or modify the reference teachings. Thus, the criteria necessary for establishing a *prima facie* case of obviousness have not been established with respect to the present claims. Therefore, Applicants respectfully request that the rejection of claims 15-28 under 35 USC § 103(a) be reconsidered and withdrawn.

V. Rejections under 35 U.S.C. § 112

The Examiner has rejected claims 15-28 under 35 USC § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. *See* Paper No. 8, page 4. The Examiner has set forth three separate grounds for this rejection, each of which is addressed in turn below.

A. Claim 15: "Active Substance for IFN-γ"

The Examiner asserted that claim 15 is ambiguous in the recitation of "active substance for IFN-γ." *See* Paper No. 8, page 4. Applicants respectfully traverse this rejection. However, solely to expedite prosecution, Applicants have amended claim 15 such that the phrase "the active substance for" is deleted. Accordingly, the rejection of claim 15 under 35 USC § 112, second paragraph, based on the recitation of "active substance for IFN-γ," has been fully accommodated by the claim amendment and is rendered moot.

B. Claim 15: Effective Dose and Release Interval of IFN-γ

The Examiner asserted that "[i]t is not clear in claim 15 if the effective dose is 50ng or 5ug over an 8 day period or 50ng or 5ug over a I/2 hour period." *See* Paper No. 8, page 4. Applicants submit that there is no ambiguity regarding the dosage and release intervals that are encompassed by claim 15. Applicants first note that, contrary to the Examiner's apparent interpretation, claim 15 does not recite "50 ng *or* 5 μg." Nor does it recite "half an hour *or* 8 days." Rather, the recitation at issue in claim 15 reads as follows: ". . . the effective dose of IFN-γ being between 50 ng *to* 5 μg and the release interval being from half an hour *to* 8 days." (Emphasis added). Thus, as the language of claim 15 makes clear, a range of dosages and release intervals are encompassed by the claim. That is, *any dosage*

amount of IFN-γ between 50 ng to 5 μg that is released over *any period* ranging from half an hour to 8 days, falls within the limits of claim 15. Accordingly, Applicants contend that claim 15 is entirely clear. Applicants therefore respectfully request that the rejection of claim 15 under 35 USC § 112, second paragraph, based on the dosage and release intervals that are recited therein, be reconsidered and withdrawn.

C. Claim 26: "Tumor Cells Charged with Peptides"

The Examiner asserted that claim 26 is ambiguous in the recitation of "tumor cells charged with peptides." *See* Paper No. 8, page 4. Applicants contend that there is no ambiguity in the recitation of this phrase and that it would be immediately and completely understood by persons of ordinary skill in the art. More specifically, Applicants assert that the phrase "tumor cells charged with peptides derived from tumor antigens" would be understood to mean tumor cells into which peptides from tumor antigens have been transferred in order to facilitate interactions between the tumor cells and a host's immune system. In support of this interpretation, Applicants note that methods for transporting peptides into cells for purposes of generating an immune response, *i.e.*, charging tumor cells with peptides, were well known in the art at the time of the invention. *See, e.g.*, Buschle, *et al. Proc. Nat'l. Acad. Sci. USA 94*:3256-3261 (1997) (cited as AS2 in the Information Disclosure Statement filed by Applicants on November 7, 2000). Since there is no lack of clarity in the language of claim 26, Applicants respectfully request that the rejection of claim 26 under 35 USC § 112, second paragraph, be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

Please substitute the following claim 15 for the pending claim 15:

15. (once amended) A tumor vaccine based on tumor antigens comprising a tumor antigen source and a release system with delayed release of [the active substance for] IFN-γ, the effective dose of IFN-γ being between 50 ng to 5 [ug] μg and the release interval being from half an hour to 8 days.

Please substitute the following claim 16 for the pending claim 16:

16. (once amended) The tumor vaccine of claim 15, wherein the effective dose of the IFN-γ is 100 ng to 2 [ug] μg.

Please substitute the following claim 17 for the pending claim 17:

17. (once amended) The tumor vaccine of claim 16, wherein the effective dose of IFN-γ is 100 ng to 1 [ug] μg.